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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,369	05/24/2007	Peter R. Brink	13533/48203	3149

26646 7590 10/28/2009

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
10/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,369	BRINK ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13 and 20-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,11,12 and 20-23* is/are rejected.

7)☒ Claim(s) *10 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed October 6, 2009.

Claims 6, 14-19, and 24 have been canceled. Claims 1, 2, 4, 5, 8, 10, 13, and 20-23 have been amended.

Claims 1-5, 7-13, and 20-23 are pending in the instant application.

Claims 1-5, 7-13, and 20-23 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawal of Finality

After careful reconsideration of the claims, a new ground(s) of rejection is made of record as detailed below. Therefore, the finality of the Office Action mailed July 6, 2009 is withdrawn.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed July 6, 2009, claims 1-24 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering an oligonucleotide into a target cell *in vitro*, the method comprising a) introducing the oligonucleotide into a donor cell and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide is delivered into the

target cell from the donor cell by traversing the gap junction, wherein the oligonucleotide is between 12-24 nucleotides in length and the gap junction channel is composed of connexin 43, does not reasonably provide enablement for a method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising a) introducing the oligonucleotide or the plasmid into a donor cell *in vitro*, and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide, the plasmid expressing the oligonucleotide or a peptide product thereof is delivered into the target cell from the donor cell by traversing the gap junction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. **This rejection is moot** against claims 6, 14-19, and 24 in view of Applicant's Amendment filed October 6, 2009 to cancel these claims. **This rejection is withdrawn** against claims 1-5, 7-13, and 20-23 in view of Applicant's Amendment filed October 6, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to recite specifically connexin 43 and to recite specific lengths of the oligonucleotide.

However, as noted above, after careful reconsideration of the claims, a new ground(s) of rejection is made of record as detailed below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 7-9, 11, 12, and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal et al. (Biochimie, 1995 Vol. 77:439-443), as evidenced by Salomon et al. (Journal of Investigational Dermatology, 1994 Vol. 103(2), Abstract only), in view of Hammond et al. (Nature Reviews. Genetics, 2001 Vol. 2:110-119).

The claimed invention is drawn to a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction, wherein the oligonucleotide is 12-24 nucleotides in length, wherein the

oligonucleotide is expressed from a plasmid, and wherein the oligonucleotide is an antisense or siRNA.

Rosenthal et al. teach a cDNA antisense oligonucleotide plasmid was delivered to human epidermal keratinocyte cells in culture (see Figure 1 and Figure 2, for example). Rosenthal et al. also teach that the human epidermal keratinocyte cells expressing the cDNA antisense oligonucleotide construct were grafted onto nude mice (see Figure 3). It should be noted that epidermal keratinocyte cells express endogenous levels of connexin 43 as evidenced by Salomon et al. (see Abstract).

In this instance, the human epidermal keratinocyte cells expressing the cDNA antisense oligonucleotide construct are the donor cells as recited in Applicant's claims. Additionally, the nude mice represent target cells that come into contact with the aforementioned donor cells as recited in Applicant's invention. It is noted that Rosenthal et al. do not explicitly state that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction. However, since the method steps recited in Applicant's claims are the same method steps as taught by Rosenthal et al., the Examiner is interpreting that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction, absent evidence to the contrary.

Applicant is reminded that the burden of establishing whether the teachings disclosed by Rosenthal et al. would have the additional function of delivering the oligonucleotide into the target cell from the donor cell by traversing the gap junction under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or

composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Also, see *In re King*, 801 F.2d 1324, 1327, 231 USPQ 136, 139 (Fed. Cir. 1986). Therefore, it falls to Applicant to determine and provide evidence that the oligonucleotide taught by Rosenthal et al. is or is not delivered into the target cell from the donor cell by traversing the gap junction as instantly claimed.

Ascertaining the differences between the prior art and the claims at issue

Rosenthal et al. do not teach that the oligonucleotide is 12-24 nucleotides in length or that the oligonucleotide is a siRNA.

Hammond et al. teach that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense. For example, on page 110, first column, Hammond

teaches that antisense methods are straightforward but suffer from "questionable specificity and incomplete efficacy". RNA interference on the other hand, "has been shown in diverse organisms to inhibit gene expression in a sequence-specific manner" (same page and column) and requires only a few molecules of dsRNA per cell to silence expression. Hammond also teaches that the RNA interference phenomenon in animals was discovered by researchers who were using antisense techniques and found that the use of double stranded instead of single-stranded RNAs reduced gene expression tenfold more efficiently (see paragraph bridging pages 110-111).

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art to devise a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction, wherein the oligonucleotide is 12-24 nucleotides in length using the teachings of Rosenthal et al. combined with the teachings and motivation of Hammond et al.

One of ordinary skill in the art would have been motivated to devise a method of delivering an oligonucleotide into a target cell comprising: a) introducing the

oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction using the teachings of Rosenthal et al. One of ordinary skill in the art would have been motivated to substitute the cDNA antisense oligonucleotide construct taught by Rosenthal et al. with an oligonucleotide that is 12-24 nucleotides in length since it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

Furthermore, one of ordinary skill in the art would have been motivated to substitute the cDNA antisense oligonucleotide construct taught by Rosenthal et al. with an oligonucleotide that is 12-24 nucleotides in length, such as a siRNA, since Hammond et al. taught that RNA interference is superior to antisense.

One of ordinary skill in art would have expected success at devising a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction since Rosenthal et al. taught the successful use and design of such a method.

One of ordinary skill in art would have expected success at the substituting the cDNA antisense oligonucleotide construct taught by Rosenthal et al. with an

oligonucleotide that is 12-24 nucleotides in length since KSR forecloses that the simple substitution of one known element for another would have yielded predictable results at the time of the invention. See recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

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Claims 1-5, 7-9, 11, 12, and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giampuzzi et al. (Journal of Biological Chemistry, 2001 Vol. 276, No:31:29226-29232), as evidenced by Valiunas et al. (Journal of Physiology, 2005 Vol:2:459-468, submitted and made of record on July 6, 2009), in view of Hammond et al. (Nature Reviews. Genetics, 2001 Vol. 2:110-119).

The claimed invention is as described above.

Determining the scope and contents of the prior art

Giampuzzi et al. teach an antisense oligonucleotide plasmid, containing the fragment from -33 to +985 of a mouse coding gene, was delivered to rat kidney cells in culture (see Figure 1 and Figure 2, for example). Giampuzzi et al. also teach that the rat kidney cells expressing the antisense oligonucleotide construct were injected subcutaneously into nude mice and found to be highly tumorigenic (see Figure 5). It should be noted that rat kidney cells constitutively express connexin 43 as evidenced by Valiunas et al. (see page 463).

In this instance, the rat kidney cells expressing the antisense oligonucleotide construct are the donor cells as recited in Applicant's claims. Additionally, the nude mice represent target cells that come into contact with the aforementioned donor cells as recited in Applicant's invention. It is noted that Giampuzzi et al. do not explicitly state that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction. However, since the method steps recited in Applicant's claims are the same method steps as taught by Giampuzzi et al., the Examiner is interpreting that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction, absent evidence to the contrary.

Applicant is reminded that the Patent Office is not a research facility. See *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) and *In re King*, 801 F.2d 1324, 1327, 231 USPQ 136, 139 (Fed. Cir. 1986) at MPEP 2112. Also, see MPEP 2112.02.

Ascertaining the differences between the prior art and the claims at issue

Giampuzzi et al. do not teach that the oligonucleotide is 12-24 nucleotides in length or that the oligonucleotide is a siRNA.

Hammond et al. is relied upon as discussed *supra*.

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art to devise

a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction, wherein the oligonucleotide is 12-24 nucleotides in length using the teachings of Giampuzzi et al. combined with the teachings and motivation of Hammond et al.

One of ordinary skill in the art would have been motivated to devise a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction using the teachings of Giampuzzi et al. One of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotide construct taught by Giampuzzi et al. with an oligonucleotide that is 12-24 nucleotides in length since it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

Furthermore, one of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotide construct taught by Giampuzzi et al. with an oligonucleotide that is 12-24 nucleotides in length, such as a siRNA, since Hammond et al. taught that RNA interference is superior to antisense.

One of ordinary skill in art would have expected success at devising a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction since Giampuzzi et al. taught the successful use and design of such a method.

One of ordinary skill in art would have expected success at substituting the antisense oligonucleotide construct taught by Giampuzzi et al. with an oligonucleotide that is 12-24 nucleotides in length since KSR forecloses that the simple substitution of one known element for another would have yielded predictable results at the time of the invention. See recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

Claims 10 and 13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 10 is considered to be free of the prior art since the prior art does not teach or fairly suggest a method of delivering an oligonucleotide into a target cell comprising: a) introducing the

oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction, wherein the oligonucleotide is 12-24 nucleotides in length, wherein the oligonucleotide is expressed from a plasmid, wherein the oligonucleotide is an antisense or siRNA, and wherein the donor cell is a cell engineered to contain connexin 43.

Claim 13 is considered to be free of the prior art since the prior art does not teach or fairly suggest a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide into a donor cell *in vitro*; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction, wherein the oligonucleotide is 12-24 nucleotides in length, wherein the oligonucleotide is expressed from a plasmid, wherein the oligonucleotide is an antisense or siRNA, and wherein the target cell is a white blood cell.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on 571-272-2914. The fax phone number for

the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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>
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October 22, 2009
/Terra Cotta Gibbs/

/Sean R McGarry/

Primary Examiner, Art Unit 1635